Answer 1:

Bibliographic Information

Effects of exemestane and tamoxifen in a postmenopausal breast cancer model. Jelovac, Danijela; Macedo, Luciana; Handratta, Venkatesh; Long, Brian J.; Goloubeva, Olga G.; Ingle, James N.; Brodie, Angela M. H. Department of Pharmacology and Experimental Therapeutics, University of Maryland School of Medicine, Baltimore, MD, USA. Clinical Cancer Research (2004), 10(21), 7375-7381. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 142:211632 AN 2004:946694 CAPLUS

Abstract

To optimize treatment strategies for postmenopausal breast cancer patients, we investigated the efficacy of the steroidal aromatase inhibitor exemestane alone or in combination with the antiestrogen tamoxifen in a xenograft model of postmenopausal breast cancer. We also detd. the effects of these agents in sequential second-line therapy and the effect of the nonsteroidal aromatase inhibitor letrozole on tumors that progressed on the above treatments. Aromatase-transfected human estrogen receptor-pos. breast cancer cells (MCF-7Ca) were grown as tumors in ovariectomized athymic mice. Animals received s.c. injection with vehicle, tamoxifen, exemestane, tamoxifen plus exemestane, and letrozole. Tumor vols. were measured weekly. All treatments were effective initially in suppressing tumor growth as first-line therapy compared with vehicle treatment. Exemestane suppressed tumor growth to a greater extent than tamoxifen. However, the combination of tamoxifen plus exemestane was more effective than either drug alone. After tumor vols. doubled on initial treatment, the mice were crossed over to receive exemestane or tamoxifen. Tumor growth slowed briefly in mice treated with tamoxifen and crossed over to exemestane, but tumor growth continued unabated in those changed from exemestane to tamoxifen. However, letrozole was effective in both groups as third-line therapy for a limited period. Letrozole as initial single agent was the best overall treatment in terms of the degree of tumor suppression and the length of effectiveness of treatment. Exemestane was more effective in controlling tumor growth than tamoxifen. In addn., the combination of exemestane plus tamoxifen was clearly more effective than sequential use of these agents in the tumor model. However, the nonsteroidal aromatase inhibitor letrozole as first-line therapy was overall the most effective treatment in controlling tumor growth.

Answer 2:

Bibliographic Information

Aromatase inhibitors in breast cancer. Brodie, Angela. Dept Pharmacology and Experimental Therapeutics, University of Maryland, School of Medicine, Baltimore, MD, USA. Trends in Endocrinology and Metabolism (2002), 13(2), 61-65. Publisher: Elsevier Science Ltd., CODEN: TENME4 ISSN: 1043-2760. Journal; General Review written in English. CAN 137:118895 AN 2002:122086 CAPLUS

Abstract

A review. Several compds. that selectively inhibit estrogen synthesis via aromatase have been developed. Steroidal substrate analogs, such as formestane and exemestane, inactivate aromatase by binding irreversibly to it. Non-steroidal inhibitors, such as the triazole compds. letrozole and anastrozole, are highly potent, reversible inhibitors with good specificity for aromatase. The intratumoral aromatase model for postmenopausal breast cancer has been used to investigate the efficacy of letrozole, anastrozole and exemestane in combination and sequentially. Combining letrozole or arimidex with tamoxifen or faslodex was not more effective than the aromatase inhibitors alone, but was more effective than tamoxifen alone. Letrozole was superior to and longer lasting than the other agents, suggesting that aromatase inhibitors control tumor growth effectively by inducing greater tumor response and extending treatment time. In addn., aromatase inhibitors can be effective in patients relapsing from tamoxifen. Because two types of aromatase inhibitors are available, steroidal enzyme inactivators and reversible non-steroidal inhibitors in sequential therapy could be useful if resistance to one type develops. Aromatase (estrogen synthesis) inhibitors have been developed. These are more effective than tamoxifen in mouse xenograft models, and current clin. data suggest the inhibitors are likely to improve breast cancer treatment.

Answer 3:

Bibliographic Information

Challenges in the endocrine management of breast cancer. Mouridsen Henning T; Rose Carsten; Brodie Angela H; Smith Ian E Department of Oncology, Rigshospitalet, Copenhagen, Denmark Breast (Edinburgh, Scotland) (2003), 12 Suppl 2 S2-19. Journal code: 9213011. ISSN:0960-9776. Journal; Article; (JOURNAL ARTICLE); General Review; (REVIEW) written in English. PubMed ID 14659138 AN 2003579108 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The goal of endocrine therapy in breast cancer is to block the action of estrogen on the tumor cells either by inhibiting estrogen from binding to the specific estrogen receptor or by inhibiting its synthesis. Tamoxifen, a selective estrogen receptor modulator, is the standard endocrine treatment for hormone receptor-positive breast cancer, both in the adjuvant and metastatic settings. Tamoxifen inhibits the binding of estrogen to the receptor, resulting in inhibition of hormone action. However, as tamoxifen is also weakly estrogenic, it may not be optimally effective and increases the risk of endometrial cancer and stroke. Furthermore, patients may be refractory or may become resistant to tamoxifen treatment. Since aromatase inhibitors (AI) block the synthesis of estrogen and have no intrinsic estrogenic activity, they have the potential to be more effective than tamoxifen. Their different mechanism of action and chemical structures may also circumvent tamoxifen resistance. Consequently, AIs are currently being evaluated as an alternative to tamoxifen treatment. A preclinical model has recently been developed to compare the efficacy of AIs and antiestrogens in different treatment schemes and to assist in the design of clinical trials. Current studies with the MCF-7Ca xenograft model are exploring the effects of combination and sequential therapy on tumor growth. The efficacy of AIs in the treatment of hormone receptor-positive breast cancer was first demonstrated in five multicenter second-line trials enrolling several hundreds of postmenopausal patients with metastatic breast cancer who had failed tamoxifen treatment. More recently, anastrozole demonstrated efficacy at least equivalent to that of tamoxifen in first-line randomized, phase III clinical trials in postmenopausal women with hormone receptor-positive or unknown metastatic breast cancer, whereas letrozole demonstrated superiority. The steroidal AI exemestane is currently under evaluation.

Letrozole is the only AI to have been studied in a randomized, phase III trial in the neoadjuvant setting. In this trial, more patients underwent breast-conserving surgery with letrozole than with tamoxifen. Smaller phase II studies also suggest that both anastrozole and exemestane are active in the neoadjuvant setting. Because neoadjuvant trials permit temporal sampling of breast tissue, substudies in the phase III trial with letrozole have examined the impact of such biomarkers as estrogen receptor, progesterone receptor and epidermal growth factor receptor family members, HER-1 and HER-2, on patient response. AIs are currently under evaluation in the adjuvant setting, and preliminary results of the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial have been reported. AIs have proven as safe as tamoxifen in trials in patients with metastatic breast cancer. Ongoing clinical trials in the adjuvant setting include companion studies of end-organ effects, particularly bone metabolism and lipid metabolism evaluations. Quality-of-life assessments are also parts of major clinical trials. A head-to-head quality-of-life assessment of anastrozole compared with letrozole demonstrated patient preference for letrozole. These assessments also clearly indicated the eagerness of patients to participate actively in treatment decisions

Answer 4:

Bibliographic Information

The intratumoral aromatase model: studies with aromatase inhibitors and antiestrogens. Brodie Angela H; Jelovac Danijela; Long Brian Department of Pharmacology & Experimental Therapeutics, School of Medicine, University of Maryland, 655 W Baltimore Street, Baltimore, MD 21201, USA. abrodie@umaryland.edu The Journal of steroid biochemistry and molecular biology (2003), 86(3-5), 283-8. Journal code: 9015483. ISSN:0960-0760. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 14623522 AN 2003545176 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Aromatase inhibitors have now been approved as first-line treatment options for hormone-dependent advanced breast cancer. When compared to tamoxifen, these aromatase inhibitors provide significant survival and tolerability advantages. However, the optimal use of an aromatase inhibitor and tamoxifen remains to be established. To date, the intratumoral aromatase xenograft model has proved accurate in predicting the outcome of clinical trials. Utilizing this model, we performed long-term studies with tamoxifen and letrozole to determine time to disease progression with each of the treatment regimens. Aromatase-transfected MCF-7Ca human breast cancer cells were grown as tumor xenografts in female ovariectomized athymic nude mice in which androstenedione was converted to estrogen and stimulated tumor growth. When tumor volumes were approximately 300 mm3, the animals were grouped for continued supplementation with androstenedione only (control) or for treatment with letrozole 10 microg per day (long-term), tamoxifen 100 microg per day (long-term), letrozole alternating to tamoxifen (4-week rotation), tamoxifen alternating to letrozole (4-week rotation), or a combination of the two drugs. Tumors of control mice had doubled in volume in 3-4 weeks. In mice treated with tamoxifen and the combination, tumor doubling time was significantly shorter (16 and 18 weeks, respectively) than with letrozole (34 weeks). Furthermore, alternating letrozole and tamoxifen treatment every 4 weeks was less effective than letrozole alone. Tumors doubled in 17-18 weeks when the starting treatment was tamoxifen and in 22 weeks when the starting treatment was letrozole. Tumors progressing on tamoxifen remained sensitive to second-line therapy with letrozole (10 microg per day). However, when mice with letrozole-resistant tumors were switched to antiestrogen treatment, tumors did not respond to tamoxifen (100 microg per day) or faslodex (1 mg per day).

This suggests that advanced breast cancers treated with letrozole may be insensitive to subsequent second-line hormonal agents. Thus, although letrozole was determined to be an effective second-line treatment option for tumors progressing on tamoxifen, antiestrogen therapy does not appear to be effective for tumors progressing on letrozole. However, response to second-line treatment was observed in a model where tumors that had progressed on letrozole were transplanted to new mice. These tumors had been allowed to grow in the presence of supplemented androstenedione but absence of letrozole. This suggests that resistance to letrozole may be reversible, allowing tumors to respond to subsequent antiestrogens and letrozole.

Answer 5:

Bibliographic Information

Preclinical evaluation of aromatase inhibitors antitumor activity. Auvray P; Bichat F; Genne P Oncodesign Biotechnology, Parc technologique de la Toison-d'Or, 28, rue de Broglie, 21000 Dijon, France Bulletin du cancer (2000), 87 Spec No 7-22. Journal code: 0072416. ISSN:0007-4551. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE); General Review; (REVIEW) written in French. PubMed ID 11250604 AN 2001184265 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Aromatase is an enzymatic complex responsible for the conversion of androgens into estrogens; these hormones are important in development, reproduction, but also in the growth of estrogen-dependent cancer. This enzyme is present in 60-70% of the breast cancer. The aromatase inhibitors are important drugs in the breast cancer treatment of postmenopausal women. In order to study their in vivo activity, animal models have been developed, e.g. rat with tumour induced by 7,12-dimethylbenz[a]anthracene, PMSG-primed immature rat or athymic nude mice with aromatase transfected MCF-7 xenograft. In this review, we were interested in preclinical results obtained with both classes: steroidal and nonsteroidal inhibitors. The former group, as substrate analogs formestane or exemestane, are irreversible, selective and long-lasting inhibitors of aromatase. The nonsteroidal molecules, such as letrozole or anastrozole, are reversible inhibitors with high affinity. Finally, knowledge of the enzyme active site, with molecular modeling and site-directed mutagenesis, could be useful to develop new inhibitor families, more specific and potent in vivo.